kb EcoRI-EcoRI cDNA fragment) of murine *Vezf1* cDNA, respectively, in pBluescript II SK (grown in DH5ÿ) and a nucleic acid, termed *mVezf1.N*, containing the aforementioned 20 kb genomic NotI-NotI fragment in pBluescript II SK (grown in DH5ÿ) , have been deposited under the terms of the Budapest Treaty with the American Type Culture Collection (ATCC), having an address of 12301 Parklawn Drive, Rockville, Maryland, 20852 on May 19, 1998 and assigned accession nos. 209873, 209874, and 209875, respectively. --

IN THE CLAIMS:

Please cancel claims 7-25 without prejudice to the prosecution of this subject matter in separate patent applications.

REMARKS

Prior to the examination of the above-captioned application, applicants respectfully request that the above amendments be made of record and the remarks made herein be considered by the Examiner.

The accompanying continuation application is filed in response to an Office Action mailed July 17, 2001 and an Advisory Action mailed January 3, 2002 in the parent application 09/083,290. Applicants respectfully request reconsideration of this application in view of the following remarks. The accompanying November 18, 2001 Declaration of Dr. Heidi Stuhlmann with an attached manuscript is offered as additional support for Applicants' invention.

Claims 1-6 are pending. Claims 7-25 have been cancelled without prejudice to the prosecution of this subject matter in separate patent applications. Applicants submit this Preliminary Amendment to continue prosecution of claims 1-6 in the instant application.

Applicants amended the specification to provide a cross-reference to related application section and to specify Applicants' claim of priority to prior continued prosecution application (CPA) filed July 5, 2001 of application Serial No. 09/083,290 filed May 22, 1998.

In the parent application the Examiner rejected pending Claims 1-6 under 35 U.S.C. §101 as unpatentable due to lack of utility. Applicants have argued that the legal standard of utility has been satisfied for the following reasons:

The Examiner asserts that *Vezf1* homology to DB1 gene does not suggest any utility for *Vezf1*, since the function of DB1 protein was unknown at the time of invention. The Examiner also asserts that function of the *Vezf1* protein is not disclosed in the specification or the art. The Examiner contends that *Vezf1* mRNA expression during angiogenesis does not indicate a function for the protein, because the specification does not teach that the *Vezf1* gene is specific to vascular disorders or endothelial cells. Furthermore, the Examiner indicates that *Vezf1* expression is not limited to expression during angiogenesis and therefore cannot be used to mark cells undergoing angiogenesis.

An invention has a well-established utility if (1) a person of ordinary skill in the art would immediately appreciate that the invention is useful based on the characteristics of the invention (e.g. properties or application of a product or process), and (2) the utility is specific, substantial and credible. Furthermore, an applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

First, the Examiner appears to be misguided by the Applicant's comparison of *Vezf1* to DB1 (specification page 6, line 15 to page 7, line 3). It is provided merely as an

example of a identified gene, that possessed 98% sequence homology with *Vezf1*. The fact that DB1 had no identified function at the time of the invention has no bearing on the utility of *Vezf1*.

Applicants disagree with the Examiner's contention that the specification does not disclose a function for *Vezf1* gene products. The specification outlines multiple uses for *Vezf1* gene products. They include the use of *Vezf1* as an endothelial cell marker (page 7, lines 11-13), its use in the development of animal models for angiogenesis (page 8, lines 1-6), its use as a diagnostic tool for vascular disorders (page 7, lines 14-21), and its use in the treatment of vascular disorders (page 8, lines 7-11). These uses described above are supported by the pattern of *Vezf1* expression in proliferating endothelial cells found in capillary networks and mature vessels. Therefore, the Applicants submit that the present invention provides sufficient examples to satisfy the requirement for specific utility.

The contents of Declaration of Dr. Heidi Stuhlmann provide substantial support for *Vezf1* as a marker for vascular endothelial cell proliferation. *Vezf1* mRNA expression localizes to populations of endothelial cells found in capillary networks in both normal and pathological states. It is highly specific to endothelial cells of capillaries and mature vessels in muscle, skeletal, lung, liver, kidney, bone marrow and heart tissue. Expression of *Vezf1* in capillaries found within induced tumors, human breast tumors, and human atherosclerotic plaques are an strong indications that *Vezf1* gene products have specific and functional roles in regulating angiogenesis. Furthermore, injury-induced proliferation of endothelial cells in rat aortas also stimulates *Vezf1* upregulation. This expression was low, but detectable in untreated arteries, became intense at 2 weeks post-injury in treated arteries, and decreased at 4 and 6 weeks post-injury in treated arteries.

The spatial and temporal correlation of *Vezf1* expression with proliferating endothelial cells within injured arteries demonstrate a specific function that is limited to angiogenic activity. Specific *Vezf1* expression during endothelial cell proliferation demonstrates that it can be used as a marker for angiogenesis. Furthermore, association with pathological endothelial cell proliferation provides the basis for practical or real world benefits. Therefore, the Applicants submit that the present invention satisfies the requirement for substantial utility.

The Applicants also contend that a person of ordinary skill in the art would immediately appreciate that the present invention is useful based on the expression pattern of *Vezf1* and that the present invention satisfies the requirement for credible utility under 35 U.S.C. §101.

<u>Conclusion</u>

In view of the above remarks and the enclosed Declaration, the Applicants submit that claims 1-6 constitute allowable subject matter. A Notice of Allowance is respectfully requested.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENT

Amendments to the paragraph beginning on page 14, line 16 and ending on page 15, line 2:

Two purified and isolated nucleic acids, together comprising *Vezf1* cDNA, termed *mVezf1.1* (3-1444) and *mVezf1.2*(1394-2820), containing nucleic acid residues 3-1444 (in a 1.444 kb EcoRI-EcoRI cDNA fragment) and 1394-2820 (in a 1.429 kb EcoRI-EcoRI cDNA fragment) of murine *Vezf1* cDNA, respectively, in pBluescript II SK (grown in DH5ÿ) and a nucleic acid, termed *mVezf1.N*, containing the aforementioned 20 kb genomic NotI-NotI fragment in pBluescript II SK (grown in DH5ÿ) , have been deposited under the terms of the Budapest Treaty with the American Type Culture Collection (ATCC), having an address of 12301 Parklawn Drive, Rockville, Maryland, 20852 on May 19, 1998 and assigned accession nos. 209873, 209874, and 209875 respectively.